REVIEW ARTICLES

Patient-derived bladder cancer xenografts: a systematic review

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Patient-derived tumor xenografts (PDTXs) are said to accurately reflect the heterogeneity of human tumors. In the case of human bladder cancer, few studies are available featuring these models. The best methodology to develop and the real value of the model remain unclear. This systematic review aims to elucidate the best methodology to establish and use PDTXs to study the characteristics and behavior of human bladder tumors. The value and potential application of these models are also addressed. A comprehensive literature search was performed to identify published studies using xenograft models directly established from human bladder cancer samples into mice. A total of 12 studies were included in the final analysis. All studies differed in design; the reported take rate varied between 11% and 80%, with the implantation via dorsal incision and with matrigel obtaining the higher take rate. Advanced stage and high-grade tumors were associated with increased take rate. Xenografts preserved the original tumor identity in the establishment phase and after serial passages. Although some studies suggest a correlation between engraftment success and clinical prognosis, evidence about the association between the response of xenografts to treatment and the clinical response of the tumor of origin is still missing. All methodological approaches resulted in the establishment of tumor xenografts with preservation of the original tumor identity but variable take rate. The time needed to establish the model and propagate xenografts to a number suitable for drug testing is the main limitation of the model, along with the success rate and lack of consistency in the early passages. Comparison between tumor response in mice and clinical outcome remains to be assessed. (Translational Research 2015;166:324–331)

Abbreviations: IP = inverted papilloma; NEBC = neuroendocrine bladder cancer; PDTX = patient-derived tumor xenografts; SCC = squamous cell carcinoma; SCID = severe combined immunodeficient; Small CC = small cell carcinoma; TCC = transitional cell carcinoma

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INTRODUCTION

Bladder cancer is the second most common genitourinary tumor, with about 386,300 new cases and 150,200 deaths estimated to have occurred in 2008 worldwide.[1] Most of these cases, approximately 75%, are nonmuscle invasive tumors for which local treatment with excision and adjuvant intravesical immunotherapy or chemotherapy are associated with high cure rates. Nevertheless, 10%–20% of these superficial tumors will recur and progress to invasive disease. Patients with muscle invasive bladder cancer have a poor prognosis with low 5-year survival rate.[2] In these cases, treatment may include cystectomy and chemotherapeutic regimens containing cisplatin.[3] The low overall response rate and unpredictable outcome for these patients have led to the search for reliable tools for assessment of prognosis and indications for therapy. The development of predictive tumor models may be a valuable aid to this purpose.

Patient-derived tumor xenografts (PDTXs) have been shown to be a highly predictive model to test standard chemotherapy and for identification of tumor types that might benefit from new treatments in clinical trials.[4] This model is established by transferring fragments of tumor derived from an individual patient into immunocompromised animals such as severe combined immunodeficient (SCID) or nude mice. Because they derive directly from patient tumor samples with minimal manipulation, the xenografts retain the cellular structure and molecular markers of the original tumors.[5] Therefore, tumor xenografts recapitulate the biological characteristics of the disease of origin and are suitable for evaluation of an individual patient's cancer chemosensitivity, providing not only an investigational platform but a potential therapeutic decision-making tool.[6-8]

Human tumor xenograft models have been developed for several types of cancers, such as lung, prostate, breast, liver, and colon carcinomas as tools for evaluation of new therapeutic strategies or individualization of cancer treatment.[7-11] However, in the case of human bladder cancer, few studies of PDTXs are available. Furthermore, to optimize and standardize the use of these models, it is important to assess if such studies clearly report the methodology and results in a way that internal reproducibility can be assessed and if the results can be systematically compared with other studies.

In this context, we conducted this systematic review on PDTX of bladder cancer to elucidate the best methodology to establish and use such models to study the characteristics and behavior of human bladder tumors.

METHODS

Search strategy. All potentially relevant articles were identified by searches done via PubMed on the Medline database using the following search terms in title or abstract: transitional cell carcinoma OR transitional cell carcinomas OR urothelial tumor OR urothelial cancer OR urothelial carcinoma OR urothelial carcinomas OR bladder tumor OR bladder cancer OR bladder cancers OR bladder carcinoma OR bladder carcinomas AND xenograft OR xenografts OR xenotransplant and the following MeSH term: animal experimentation. All relevant articles published up to February 2014 were selected and no limits were introduced for the search strategy. Furthermore, this electronic search was complemented by hand searching the references listed in any included study.

Eligibility criteria. The following criteria had to be met for a study to be included in this review: xenograft model directly established from human bladder cancer samples into mice, regardless of bladder cancer grade or stage. References not written in English or those that were reviews, editorials, or letters were excluded. Any selected reference for which a full text report was not available after contact with dedicated libraries or with the corresponding author was also excluded.

All retrieved references were screened for eligibility based on title and abstract review by 2 of the authors. All references deemed potentially eligible were retrieved for full text assessment of eligibility by 2 of the authors.

Data extraction. Data extraction was performed by 2 authors with the use of a predefined data collection form. The following data were collected from each reference: article identification details (title, authors, and publication date); methodological details (study design, number and characteristics of mice used, and number of patients and primary tumor sample characteristics); tumor take rate (defined as the percentage of mice with xenograft growth divided by the total number of mice implanted, should more than 1 fragment be implanted per mouse into distinct locations, each was considered as independent study units for this end point); success rate (defined as the number of xenografts obtained per human tumor sample used); lag period; number of passages; xenograft histologic and molecular characteristics; and comparison of xenograft characteristics with the original human tumor. When analyzing tumor take rate and success rate, engraftment was considered successful when a progressive tumor growth in man-to-mouse generation passage reached a tumor volume of at least 100 mm^3. At this point, the growing tumor can be clearly identified and measured and the risk of spontaneous regression is low.